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| 10/677,131 | 09/30/2003 | Robert F. Balint | 021167-001100US | 3895 |

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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

| EXAMINER | |
|---|---|
| WESSENDORF, TERESA D | |
| ART UNIT | PAPER NUMBER |
| 1639 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 04/20/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/677,131 | BALINT ET AL. | |
| | Examiner | Art Unit | |
| | T. D. Wessendorf | 1639 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *33,35-40,43-45,48,50-55,58-60 and 63-68* is/are pending in the application.

4a) Of the above claim(s) *38,40,43-45,53,55,58-60,65 and 68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33,35-37,39,48,50-52,54,63,64,66 and 67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

***Election/Restrictions***

Applicant's election with traverse of Group I (claims 33, 35-37, 39, 48, 50-52, 54; 63, 64, 66, and 67) in the reply filed on 1/19/2007 is acknowledged. The traversal is on the ground(s) that Applicants again respectfully request reconsideration of the withdrawal of claims 42, 43, 44, 45, 58, 59, and 60 as non-elected species for reasons explained at page 8 of Applicants' August 29, 2006 response. The foregoing election is made with traverse. As the Examiner noted, claims 33 and 48 are generic. Applicants are entitled to examination of the claims that were filed ("it is improper for the Office to refuse to examine that which applicant regards as their invention..." MPEP § 803.02, cited regarding Markush claims). The Patent Office has provided procedures for examination of generic claims. Applicants urge that the proper restriction is a species election or a restriction requirement that designates claims 33 and 48 as generic linking Claims. Applicants therefore request reconsideration of the group election requirement. This is not found persuasive for the reasons already stated in the Office action of 2/23/2006. The withdrawn claims 42-45 and 58-60 are drawn to non-elected species as being drawn to a hybrid

antibody. Therefore, these claims have not been examined on the merits in the Office action of 2/23/2006.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, mailed on 11/15/2006, for which the present Group I was elected that includes the new claims 66-67, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

Claims 38, 40, 43-45, 53, 55, 58-60, 65 and 68 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 1/19/2007.

Note as correctly noted by Applicants claims 35-37, 39, 50-52, and 54 are also under examination albeit the Office Summary of 11/15/2006 recited only the claims 33, 48, and newly added claims 63-68 under restriction. See the status of the claims below.

***Status of Claims***

Claims 33, 35-40, 43-45, 48, 50-55, 58-60 and 63-68 are pending.

Claims 38, 40, 43-45, 53, 55, 58-60, 65 and 68 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

Claims 33, 35-37, 39, 48, 50-52, 54, 63-64 and 66-67 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

***Withdrawn Rejections***

In view of the amendments to the claims and applicants' arguments, the rejection of the claims under 35 USC, first and second paragraphs and 35 USC 102 over Dove are withdrawn.

***Double Patenting***

Claims 33, 35-37, 39, 48, 50-52, 54, 63-64 and 66-67, as amended, are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-29 of copending Application No. 10/208,730 ('730 application). Although the conflicting claims are not identical, they are not patentably distinct from each

other because the instant claimed method is encompassed by the broad claimed method of the '730 application. The instant claimed method which recites a recombinant method would be included in the broad method of the '730 application.

***Response to Arguments***

Applicants will gladly consider filing a terminal disclaimer should the conflicting claims be allowed before allowable claims have been identified in the current application.

In the absence of a terminal disclaimer the rejection is maintained.

***Claim Rejections - 35 USC § 103***

Claims 33, 35, 37, 48, 50, 52, 63-64 and 66-67, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Balint (WO 00/71702) in view of Nandabalan et al. (6057101); and further in view of Strynadka et al (Nature Structural Biology) and Wigley et al (Nature Biotechnology) and Anderson et al(6974684).

Balint et al teaches a method of detecting protein interactions or inhibitors of these interactions using a fragment complementation system which is characterized by using reporter fragment pairs fused to a first and a second member, wherein binding of the first polypeptide to the second

polypeptide results in the functional reconstitution of the fragment pair into a marker protein, and the interaction of the two polypeptides can be detected. Thus, folding of the reporter enzyme from its fragments is catalyzed by the binding of the test proteins to each other, and is detected as reconstitution of enzyme activity. Balint et al also teaches appropriate host cells for the application of the subject inventions, which include the bacterial cell population such as E. coli. Balint et al also teaches examples wherein the polypeptide interactor domains can be selected from (i) single-chain antibody Fv fragments (scFv) (see example 1 in particular), wherein scFv is comprised of antibody heavy chain and light chain variable regions (VH and VL) tethered into a continuous polypeptide by linker or (ii) an antibody light chain V-regions (VL) (see example 2 in particular); and (iii) the reporter fragment molecules to be the beta-lactamase (197 and 198 fragments (interaction-dependent TEM-1 b-lactamase fragments). When the two vectors (fusion proteins), as mentioned above, are expressed in a bacterial cell the two b-lactamase fragments cooperatively produce selectable activity in a manner that is strictly dependent on the specific interaction between the two polypeptide domains. Thus, if a fragment pair library of a non-phenotypic protein is expressed as fusions to the interaction-

dependent TEM-1 (b-lactamase fragments), it is expected that only those fragment pairs (the polypeptide domains) which associate and fold into the native conformation will provide sufficient docking function to facilitate selectable b-lactamase activation. Balint et al further teaches that such target interactions identified using interaction-dependent b-lactamases could be used to screen for inhibitors of the interaction of the two polypeptide interactor domains (see page 20, lines 9-11 in particular). Thus Balint et al teaches a system in which a target molecule is identified in a bacterial cell population, wherein the target molecule may inhibit the interaction between two polypeptide interactor domains and the inhibition of interaction is indicated by the absence of the b-lactamase activation. Balint et al does not specifically teach the method wherein the polypeptide domains are linked to a reporter and an inhibitor of the reporter molecule, wherein the activation of the reporter molecule indicates the inhibition of the interaction of polypeptide domains and vice versa. Balint et al also does not teach the markers to a B-lactamase and the b-lactamase inhibitor protein (BLIP). These deficiencies are made up for in the teachings of Wigley et al, Nandabalan et al and Strynadka et al. Wigley et al teach that such protein complementation assays require some degree of optimization for

each target protein analyzed (please see Wigley et al, page 134 column 2 last paragraph in particular). For example, expression levels as well as kinetics of aggregation of the (fusion proteins will affect the readout over the course of the experiment. In special cases, the alpha-fragment may be sterically occluded in the folded fusion protein, thereby hindering its ability to complement the enzyme activity. Conversely, the (alpha-fragment could remain accessible for some degree of complementation, even when associated in large aggregates, perhaps accounting for the background activity observed. Thus, the central problem in such approaches may be that subunits, even if weakly associating, are always capable of doing so to some extent, meaning that there is a constant background of spontaneous assembly. Nandabalan et al teaches an embodiment in which the interaction assay is carried out in a prokaryotic cell and in which fusion proteins to a transcriptional inhibition domain are used as one of the population of proteins, both the DNA binding domain fusion population can be fusions to the cl repressor. In this embodiment, interaction of two fusion proteins promotes oligomerization of the cl DNA binding domain sufficient to cause DNA binding and inhibition of transcription (see column 12 lines 59-68 and column 13 lines 1-16, in particular). Nandabalan et al

also teaches that the inhibitors that interfere with the protein-protein interaction can be identified with this system. Thus, Nandabalan et al teaches that the DNA binding domain of a reporter and the transcription activator/inhibition domain(auto-inhibited responder complex, as claimed) each can be utilized as markers fused to the polypeptide domains of interest, for the purposes of identifying a molecule that inhibits the interaction of polypeptide domains, wherein the interaction of the two polypeptide domains is indicated by inhibition of the reporter molecule and the inhibition of the interaction of the two polypeptide domains is indicated by an active reporter. Strynadka et al teaches a novel 165 amino acid TEM-1 b-lactamase inhibitor protein (BLIP) and that the ability of BLIP to adapt to a variety of lactamases is most likely due to an observed flexibility between two domains of the inhibitor and to an extensive layer of water molecules entrapped between the enzyme and inhibitor (see abstract, in particular). Strynadka et al teach the inhibition of b-lactamases by BLIP using crystallographic studies including that the kinetic analyses of BLIP with a wide spectrum of b-1actamases characterize it as the most potent inhibitor of the enzyme. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method for

identifying a target molecule in a gram negative bacterial cell population, comprising introducing into the population of cell expression vector(s) comprising a nucleic acid sequence encoding a first binding pair member linked to a b-lactamase molecule and further comprising a nucleic acid sequence encoding a second binding pair member linked to b-lactamase inhibitor protein (BLIP); wherein the b-lactamase molecule is inhibited when the binding pair members interact; wherein a target molecule that binds to at least one binding pair member prevents BLIP from binding to the b-lactamase molecule, thereby activating the b-lactamase; wherein the first or second binding pair members are antibodies. One of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have produced a method for identifying a target molecule in a gram negative bacterial cell population, comprising introducing into the population of cell expression vector(s) comprising a nucleic acid sequence encoding a first binding pair member linked to a b-1actamase molecule and further comprising a nucleic acid sequence encoding a second binding pair member linked to b-1actamase inhibitor protein (BLIP); wherein the b-lactamase molecule is inhibited when the binding pair members interact; wherein a target molecule that binds to at least one binding pair member prevents BLIP from binding to the b-

lactamase molecule, thereby activating the b-lactamase; wherein the first or second binding pair member are antibodies in view of Balint et al, Wigley et al, Nandabalan et al and Strynadka et al because Balint et al teaches a method of detecting protein interactions or inhibitors of these interactions using a fragment complementation system which is characterized by using reporter fragment pairs fused to a first and a second interacting polypeptide members, wherein binding of the first polypeptide to the second polypeptide results in the functional reconstitution of the fragment pair into a marker protein, and the interaction of the two polypeptides can be detected, and because Wigley et al teaches that such protein complementation assays require some degree of optimization for each target protein analyzed and depend on the expression levels as well as kinetics of aggregation of the fusion proteins will affect the readout over the course of the experiment in such a way that the fragment may be sterically occluded in the folded fusion protein, thereby hindering its ability to complement the enzyme activity and conversely, the fragment could remain accessible for some degree of complementation, even when associated in large aggregates, perhaps accounting for the background activity observed. In addition, it would have been obvious because Nandabalan et al teaches an embodiment in which the interaction

assay is carried out in a prokaryotic cell and in which fusion proteins to a transcriptional inhibition domain are used as one of the population of proteins wherein the interaction of two fusion proteins is sufficient to inhibition of transcription and subsequently the expression of the reporter, and because Strynadka et al teach the inhibition of b-1actamases by BLIP using crystallographic studies including that the kinetic analyses of BLIP with a wide spectrum of 13-1actamases characterize it as the most potent inhibitor of the enzyme. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have produced a method which detects a target molecule that inhibits the interaction of a first polypeptide interactor domain with a second polypeptide interactor domain by bringing into close proximity members of a fragment pair of a marker protein as taught by Balint et al, wherein the marker fragment pair is replaced in order to avoid the possibility a weak interaction of the two fragments leading to a constant background of spontaneous assembly as taught by Wigley et al wherein the parent marker protein reassembly following interaction of the heterologous interactor domains can be detected by the inhibition of the reporter molecule as taught by Nandabalan et al. Further, it would have been obvious to one of ordinary skill

in the art at the time the invention was made to have modified the method of Balint et al to further comprise b-1actamase and b-lactamase inhibitor protein (BLIP), in the place of the two [b-1actamase fragments, as the marker proteins (to avoid constant background of spontaneous assembly of the two fragments as taught by Wigley et al) because Strynadka et al. teaches the inhibition of b-1actamases by BLIP using crystallographic studies including the kinetic analyses of BLIP with a wide spectrum of b-1actamases which characterize it as the most potent inhibitor of the enzyme. Thus, there would be an advantage to substituting the two b-lactamase fragments in the method taught by Balint et al with b-1actamase and b-lactamase inhibitor protein (BLIP) as the marker proteins as taught by Strynadka et al because Wigley et al taught that the enzyme fragment complementation assays may lead to a constant background of spontaneous assembly, because the subunits, even if weakly associating, are always capable of doing so to some extent. Additionally, one of ordinary skill in the art at the time of invention was made would have combined the method taught by Balint et al with the b-1actamase and b-1actamase inhibitor protein (BLIP) as the marker proteins substituted for the b-1actamase fragments with the method taught by Nandabalan et al because Nandabalan et al teaches a method of identifying a

molecule that inhibits the interaction of polypeptide domains, wherein the interaction of the two polypeptide domains is indicated by inhibition of the reporter molecule and the inhibition of the interaction of the two polypeptide domains is indicated by an active reporter. Thus, it would have been obvious to one skilled in the art at the time the invention was made to have produced a method for identifying a target molecule in a gram negative bacterial cell population, comprising introducing into the population of cell expression vector(s) comprising a nucleic acid sequence encoding a first binding pair member linked to a b-1actamase molecule and further comprising nucleic acid sequence encoding a second binding pair member linked to b-1actamase inhibitor protein (BLIP); wherein the b-1actamase molecule is inhibited when the binding pair members interact; wherein a target molecule that binds to at least one binding pair member prevents BLIP from binding to the b-1actamase molecule, thereby activating the b-1actamase; wherein the first or second binding pair member are antibodies in view of Balint et al, Wigley et al, Nandabalan et al and Strynadka et al. Therefore the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Claims 36, 39, 51 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over over Balint (WO 00/71702) in view of Nandabalan et al. (6057101); and further in view of Strynadka et al (Nature Structural Biology) and Wigley et al (Nature Biotechnology) as applied to claims 33, 35, 37, 48, 50, 52, 63-64 and 66-67 above, and further in view of Anderson et al.

Balint does not teach Fab fragments. However Anderson discloses at col. 33,lines 50-67:

> In addition, methods can be adapted for the construction of Fab expression libraries (see e.g., Huse, et al., 1989 Science 246: 1275-1281) to allow rapid and effective identification of monoclonal Fab fragments with the desired specificity for a protein or derivatives, fragments, analogs or homologs thereof. Antibody fragments that contain the idiotypes to a protein antigen may be produced by techniques known in the art including, but not limited to: (i) an F(ab')2 fragment produced by pepsin digestion of an antibody molecule; (ii) an Fab fragment generated by reducing the disulfide bridges of an F(ab')2 fragment; (iii) an Fab fragment generated by the treatment of the antibody molecule with papain and a reducing agent and (iv) Fv fragments.

It would have been obvious to use another antibody fragment, Fab, in the method of Balint instead of scFV in view of the teachings of Anderson, above, i.e., for a rapid and effective identification of monoclonal Fab fragments with the desired specificity for a protein thereof.

No claim is allowed.

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw
April 13, 2007